IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

MEADE, Christopher J.M. et al. Examiner: Eric Olson

Serial No.: 10/614,365 Group Art Unit: 1623

Filed: June 7, 2003 Confirmation No.: 7867

Title: PHARMACEUTICAL COMPOSITIONS BASED ON ANTICHOLINERGICS AND PDE-IV INHIBITORS

BRIEF ON APPEAL UNDER 37 C.F.R. § 41.37

Mail Stop - APPEALS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is an appeal from the decision of the Examiner finally rejecting claims 1, 2, 4, 5, 7-11, 13, 19-38, 43 and 44 of the above-identified application.

(1) REAL PARTY IN INTEREST

The application is assigned of record to Boehringer Ingelheim Pharma GmbH & Co. KG, who is the real party in interest herein.

(2) RELATED APPEALS AND INTERFERENCES

Appellants, their legal representative and the assignee are not aware of any related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the instant appeal.

(3) STATUS OF THE CLAIMS

Claims rejected:	Claims 1, 2, 4, 5, 7-11, 13, 19-38, 43 and 44.
Claims allowed:	(none)
Claims canceled:	Claims 3, 6, 12, 14-18 and 39-42.
Claims withdrawn:	(none)
Claims on Appeal:	Claims 1, 2, 4, 5, 7-11, 13, 19-38, 43 and 44 (Copy of claims on appeal in attached Appendix).

(4) STATUS OF AMENDMENTS

An Amendment after the Final Rejection was proposed by Appellants on April 23, 2007, and was entered for purposes of this appeal. See Box 7 of the Advisory Action mailed May 4, 2007. As a result of entry of the Amendment, the rejection under 35 U.S.C. §112, second paragraph, made in the Final Rejection was overcome. See Box 5 of the Advisory Action mailed May 4, 2007.

An Amendment after the Final Rejection was also proposed by Appellants March 22, 2007, but was not entered. However, the Terminal Disclaimer that was filed concurrently with the amendment should have automatically been entered.

(5) SUMMARY OF CLAIMED SUBJECT MATTER

Appellants' invention (sole independent claim 1) is directed to a pharmaceutical composition, which is in the form of an inhalable aerosol, solution or suspension; see, e.g., page 1, lines 11-13, and page 8, lines 15-21, of the instant specification. The solution comprises one or more anticholinergics of formula **1** shown in claim 1, on appeal; see, e.g., page 2, lines 8-20, of the instant specification. The composition further comprises one or

more PDE-IV inhibitors, (**2**), selected from enprofylline, theophylline, roflumilast, methanesulfonic acid 2-(2,4-dichlorophenylcarbonyl)-3-ureidobenzo-furan-6-yl ester, tofimilast, pumafentrine, (3-(3-cyclopentyloxy-4-methoxybenzyl)-6-ethylamino-8-isopropyl-3H purine hydrochloride), N-(3,5-dichloro-1-oxidopyridin-4-yl)-8-methoxy-2-(trifluoromethyl)quinoline-5-carboxamide, (N-(3,5-dichloro-4-pyridinyl)-2-[1-(4-fluorobenzyl)-5-hydroxy-1H-indol-3-yl]-2-oxoacetamide), N-(3,5-dichloro-1-oxo-pyridin-4-yl)-4-difluoromethoxy-3-cyclopropylmethoxybenzamide and the tricyclic nitrogen heterocycles of formula **2a** shown in claim 1 on appeal; see, e.g., page 3, line 20, to page 4, line 17, of the instant specification. Each of the PDE-IV inhibitors is optionally in the form of a racemate, an enantiomer, a diastereomer, mixtures of enantiomers or diastereomers, a tautomer, or a pharmacologically acceptable acid addition salt thereof; see, e.g., page 4, lines 14-17, of the instant specification. The composition further comprises a solvent selected from the group consisting of water, ethanol and a mixture of water and ethanol; see, e.g., page 17, lines 11-12, of the instant specification. The application is also directed to the preferred embodiments of the dependent claims on appeal and to a method of treating an inflammatory or obstructive disease of the respiratory tract comprising administering to a patient in need of such treatment a therapeutically effective amount of a pharmaceutical composition, as claimed; see, e.g., page 9, lines 8-10, of the instant specification.

(6) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The following grounds of rejection are requested to be reviewed on appeal. For each ground of rejection, any separate consideration of the claims subject to that rejection are indicated.

1. The rejection of claims 1, 2, 4, 5, 7-11, 13, 19-38, 43 and 44, on appeal, under

35 U.S.C. §103, as allegedly being obvious over Knowles (WO 03/011274) in view of Meissner (U.S. Patent No. 6,706,726) further in view of Hill (U.S. Patent No. 6,060,069).

2. The Provisional obviousness-type double patenting rejection of claims 1, 2, 4, 5, 7 and 43 over claims 1-13 of US Ser. No. 10/613,783 in view of claims 1-8, 11 and 21-23 of U.S. Patent No. 6,706,726.

(7) ARGUMENT

1. Claims 1, 2, 4, 5, 7-11, 13, 19-38, 43 and 44, on appeal, are not obvious to one of ordinary skill in the art under 35 U.S.C. §103 over Knowles (WO 03/011274) in view of Meissner (U.S. Patent No. 6,706,726) further in view of Hill (U.S. Patent No. 6,060,069).

Knowles discloses compositions containing a PDE 4 inhibitor and an anticholinergic which is particularly an M_1, M_2, M_1/M_2 or M_3 receptor antagonist; see, e.g., page 1, lines 3-7. Particularly, the M_1, M_2, or M_1/M_2 receptor antagonists are pointed out; see, e.g., page 5, lines 2-31. Knowles first and foremost discusses (see, e.g., page 4, line 28, to page 5, line 17) four specific compounds (atropine, homatropine, hyoscyamine and scopolamine). However, Knowles also lists tiotropium and its bromide salt; see, e.g., page 5, lines 22-23, and the specific examples. As acknowledged in the Final action (page 5), Knowles does not disclose a pharmaceutical composition containing a compound within formula 1 of claim 1, on appeal, and a PDE 4 inhibitor. Also, Knowles discloses no compound which falls within formula of claim 1, on appeal.

Meissner discloses compounds of their general formula 1 (see, col. 1, lines 10-30) as being anticholinergics. The Meissner formula generically encompasses formula 1 of appellants' claim 1 and the compound shown in Meissner's Example 1 is within the scope of

formula 1 of appellants' claim 1. However, Meissner provides no teaching or suggestion of the use of its anticholinergics of formula 1 together with PDE-4 inhibitors.

Hill was relied upon in the Final action for suggesting certain dependent claim embodiments regarding particular excipients in the compositions. Hill provides no suggestions to make up for the deficiencies of the combination of Knowles and Meissner to suggest appellants' invention, as discussed below. Hill provides no suggestion of combining a particular compound within Meissner's formula 1, as an anticholinergic, with the PDE-4 inhibitor compounds of Knowles.

The primary basis for the obviousness rejection alleged in the Final action is that one of ordinary skill in the art would have been motivated to prepare a composition using a specific anticholinergic selected from Meissner in place of the specific anticholinergic tiotropium disclosed in Knowles because it is also an anticholinergic and is structurally similar to tiotropium (see, e.g., page 6, last sentence, and the "Response to Argument" section at pages 8-9, of the Final action).

Appellants respectfully disagree that tiotropium disclosed in Knowles and appellants' compounds of formula 1 are of such similar structure that one of ordinary skill in the art would consider them to have the same or similar properties and be interchangeable. Referring to the formulae shown on page 9 of the Final action, it can be seen that there are five significant structural differences between these compounds:

1) - the functional -OH group in tiotropium is replaced with a methyl group in appellants' formula 1,

2) & 3) - each of two 5-membered rings in tiotropium are replaced with 6-membered rings in appellants' formula 1, and

4) & 5) - in each of these two replaced rings, the sulfur hetero group in

tiotropium is removed in appellants' formula 1, such that carbocyclic instead of heterocyclic rings are provided.

There is no basis on the record to assume that such significant changes would not effect the properties of the compounds and that these compounds would be interchangeably useful. To the contrary, it is pointed out that tiotropium was known in the art before the Meissner patent was obtained and that Meissner obtained their patent with claims covering compounds of formula I in view of this knowledge. Thus, a determination was made in issuing the Meissner patent that compounds, such as formula I, particularly with two phenyl groups, were patentably distinct over known compounds such as tiotropium, having two thiophene groups. In any event, the number of structural differences, on its face, is such that no presumption can be made that the compounds would have the same or similar properties. Such presumptions, in previous case law, were only made where the structures were adjacent homologs, such as methyl to ethyl. That is certainly not the case here. There is no legal basis to make such presumption where the structures have multiple and significant distinctions as here, i.e., replacing -OH with methyl and replacing each of two heterocyclic 5-membered thiophene rings with carbocyclic 6-membered phenyl rings.

It is further argued in the Final action that tiotropium is closer in structure to appellants' formula 1 compound than the other compounds more specifically pointed out by Knowles (e.g., atropine and scopolamine) and that this supports using appellants' formula 1 compound as the anticholinergic in Knowles. Appellants do not agree. Even if tiotropium is closer in structure to appellants' formula 1 than the other Knowles compounds, this in no way supports that tiotropium is sufficiently closely structurally similar to appellants' formula 1 compound that one of ordinary skill in the art would reasonably expect them to have the same or similar properties and be interchangeable. As pointed out above, tiotropium still has

significant structural differences from the compounds of appellants' formula 1.

Appellants urge that there is no proper basis provided in the Final action to support the interchangeability based on structural similarity alleged in the Final action as motivating the combination of references. Thus, the burden of proving obviousness is not met.

When considering the cited prior art as a whole, the following further bases are provided that support nonobviousness and direct one of ordinary skill in the art away from a reasonable expectation of success in interchanging the Meissner compounds for the anticholinergics of Knowles.

Knowles only mentions tiotropium within the scope of many other compounds. Knowles more prominently directs one of ordinary skill in the art towards other compounds; see, e.g., page 4, line 28, to page 5, line 17, of Knowles and the four specific compounds highlighted there (atropine, homatropine, hyoscyamine and scopolamine). These compounds are even more structurally distinct from appellants' formula 1 of claim 1 than tiotropium. The structures of these 4 anticholinergics lack a significant structural feature of Meissner's and appellants' compounds. These compounds have only one benzene ring where the Meissner compounds and appellants' formula 1 have two benzene rings on a single carbon. These Knowles compounds have an additional $-CH_2OH$ group rather than a further benzene ring. Like tiotropium, these 4 anticholinergics also lack an additional methyl group on the carbon which has the two benzene rings, and lack an additional methyl substituent on the nitrogen in the polycyclic ring which creates an ammonium group and provides for the anion. Thus, like tiotropium they have several significant structural differences. The suggestion in Knowles to use these even more distinct compounds further directs one of ordinary skill in the art away from compounds of appellants' formula 1, rather than towards them.

Also, Knowles teaches that a specific type of anticholinergic is desired which has a certain M_1 and M_2 receptor antagonist activity; see the paragraph bridging pages 4-5 of Knowles. Meissner provides no disclosure as to whether its compounds possess such antagonist activity. Thus, whether or not the compounds actually possess such activity, the failure of Meissner to teach such activity further detracts from any reasonable expectation of success by one of ordinary skill in the art in substituting the Meissner compounds, particularly selecting the specific compound of Meissner's Example 1, into the Knowles compositions.

Meissner also directs one of ordinary skill in the art away from interchanging the Knowles and Meissner anticholinergics and away from a reasonable expectation that such compounds would exhibit the same or similar properties. Meissner refers to compounds of the type disclosed as anticholinergics in Knowles – i.e., benzilic acid esters – in its Background section (col. 1, line 33, to col. 2, line 26) and discloses that such compounds are deficient in meeting the requirements desired for the Meissner invention. Thus, Meissner's invention was purposefully directed to structurally distinct compounds with distinct properties.

Particularly in view of the above two paragraphs, appellants urge that the cited references are directly contrary to the presumption which is made as the basis for the rejection, i.e., that the Meissner anticholinergics could be substituted for the Knowles anticholinergics with the expectation that the same or similar properties would be obtained. Although both teach compounds which are broadly considered anticholinergics, Knowles and Meissner each teach that there are significant distinctions between compounds generally known as anticholinergics and that they cannot be reasonably expected to be interchangeable merely on the basis of being broadly classified as anticholinergics. For example, Knowles

expresses a preference to certain benzilic acid ester compounds which have M_1, M_2, or M_1/M_2 receptor antagonist activity and Meissner teaches away from the use of benzilic acid esters.

Further directing one of ordinary skill in the art away from appellants' invention is the fact that Meissner does not suggest the use of its anticholinergics of formula 1 together with PDE-4 inhibitors.

In view of all of the above, appellants strongly urge that the cited prior art does not provide a reasonable suggestion to one of ordinary skill in the art to make the particular combination of a compound of formula 1 of the instant claims together with a specific PDE-4 inhibitor, as recited in claim 1. To the contrary, the teachings of the references considered as a whole would have pointed one of ordinary skill in the art away from making such specific combination. Thus, it is urged that the combined teachings of Knowles, Meissner and Hill, considered as a whole, fail to suggest the claimed invention to one of ordinary skill in the art. Thus, the rejection under 35 U.S.C. §103 should be reversed.

2. The Provisional obviousness-type double patenting rejection of claims 1, 2, 4, 5, 7 and 43 over claims 1-13 of US Ser. No. 10/613,783 in view of claims 1-8, 11 and 21-23 of U.S. Patent No. 6,706,726 was overcome by the filing of a Terminal Disclaimer.

Appellants filed a Terminal Disclaimer directed to the 10/613,783 application and accompanying fee with their Reply After Final Rejection filed March 22, 2007. The Terminal Disclaimer overcomes the obviousness-type double patenting rejection and, thus, the rejection should be reversed.

For all of the above reasons, it is urged that the decision of the Examiner rejecting claims , on appeal, is in error and should be reversed.

Respectfully submitted,

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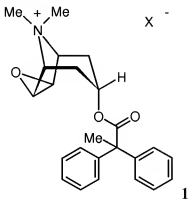
JAS:cak

CLAIMS APPENDIX

1. A pharmaceutical composition, which is in the form of an inhalable aerosol, solution or suspension, comprising:

one or more anticholinergics of formula **1**

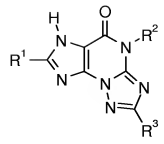


1

wherein

X^- denotes an anion with a single negative charge,

one or more PDE-IV inhibitors, (**2**), selected from enprofylline, theophylline, roflumilast, methanesulfonic acid 2-(2,4-dichlorophenylcarbonyl)-3-ureidobenzo-furan-6-yl ester, tofimilast, pumafentrine, (3-(3-cyclopentyloxy-4-methoxybenzyl)-6-ethylamino-8-isopropyl-3H purine hydrochloride), N-(3,5-dichloro-1-oxidopyridin-4-yl)-8-methoxy-2-(trifluoromethyl)quinoline-5-carboxamide, (N-(3,5-dichloro-4-pyridinyl)-2-[1-(4-fluorobenzyl)-5-hydroxy-1H-indol-3-yl]-2-oxoacetamide), N-(3,5-dichloro-1-oxo-pyridin-4-yl)-4-difluoromethoxy-3-cyclopropylmethoxybenzamide and the tricyclic nitrogen heterocycles of formula **2a**



2a

wherein

R^1 is C_1-C_5-alkyl, C_5-C_6-cycloalkyl, phenyl, benzyl or a 5- or 6-membered, saturated or unsaturated heterocyclic ring which contains one or two heteroatoms selected from oxygen and nitrogen;

R^2 is C_1-C_5-alkyl or C_2-C_4-alkenyl;

R^3 is C_1-C_5-alkyl which is optionally substituted by C_1-C_4-alkoxy, C_5-C_6-cycloalkyl, phenoxy or a 5- or 6-membered, saturated or unsaturated heterocyclic ring which contains one or two heteroatoms selected from oxygen and nitrogen; C_5-C_6-cycloalkyl, phenyl or benzyl, each optionally substituted by C_1-C_4-alkoxy,

each optionally in the form of a racemate, an enantiomer, a diastereomer, mixtures of enantiomers or diastereomers, a tautomer, or a pharmacologically acceptable acid addition salt thereof, and

a solvent selected from the group consisting of water, ethanol and a mixture of water and ethanol.

2. A pharmaceutical composition according to claim 1, wherein X^- denotes an anion selected from chloride, bromide, iodide, sulphate, phosphate, methanesulphonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate and p-toluenesulphonate.

4. A pharmaceutical composition according to claim 1, wherein in the compound of formula **1**, X^- is a negatively charged anion selected from chloride, bromide, 4-toluenesulphonate and methanesulphonate.

5. A pharmaceutical composition according to claim 1, wherein in the compound of formula **1**, X^- denotes bromide.

7. A pharmaceutical composition according to claim 1, wherein **2** is selected from enprofylline, roflumilast, (N-(3,5-dichloro-4-pyridinyl)-2-[1-(4-fluorobenzyl)-5-hydroxy-1H-indol-3-yl]-2-oxoacetamide), N-(3,5-dichloro-1-oxo-pyridin-4-yl)-4-difluoromethoxy-3-cyclopropylmethoxybenzamide and the tricyclic nitrogen heterocycles of formula **2a**.

8. A pharmaceutical composition according to claim 1, wherein the weight ratio of **1** to (**2**) is in the range from 1:100 to 100:1.

9. A pharmaceutical composition according to claim 1, wherein the weight ratio of **1** to (**2**) is in the range from 1:80 to 80:1.

10. A pharmaceutical composition according to claim 1, wherein a single dose for administration corresponds to a dose of the active substance combination **1** and (**2**) of 0.01 to 10000µg

11. A pharmaceutical composition according to claim 1, wherein a single dose for administration corresponds to a dose of the active substance combination **1** and (**2**) of 0.1 to 2000µg.

13. A pharmaceutical composition according to claim 1, wherein it is a formulation selected from propellant-containing inhalable aerosols and propellant-free inhalable solutions or suspensions.

19. A pharmaceutical composition according to claim 13, wherein it is a propellant-containing inhalable aerosol which contains **1** and (**2**) in dissolved or dispersed form.

20. A propellant-containing inhalable aerosol according to claim 19, containing a propellant gas selected from a hydrocarbon or halohydrocarbon.

21. A propellant-containing inhalable aerosol according to claim 19, containing a propellant gas selected from n-propane, n-butane, isobutene, chlorinated and/or fluorinated derivatives of methane, ethane, propane, butane, cyclopropane or cyclobutane.

22. A propellant-containing inhalable aerosol according to claim 20, wherein the propellant gas is TG134a, TG227, or a mixture thereof.

23. A propellant-containing inhalable aerosol according to claim 19, which further comprises one or more other ingredients selected from cosolvents, stabilisers, surfactants, antioxidants, and lubricants.

24. A propellant-containing inhalable aerosol according to claim 19, wherein it contains up to 5 wt.-% of active substance **1** and/or (**2**).

25. A pharmaceutical composition according to claim 1, wherein the composition is a propellant-free inhalable solution or suspension.

26. An inhalable solution or suspension according to claim 25, wherein the pH is 2 - 7.

27. An inhalable solution or suspension according to claim 25, wherein the pH is 2 – 5.

28. A pharmaceutical composition according to claim 1, wherein the composition further comprises an acid ~~is~~ selected from hydrochloric acid, hydrobromic acid, nitric acid, sulphuric acid, ascorbic acid, citric acid, malic acid, tartaric acid, maleic acid, succinic acid, fumaric acid, acetic acid, formic acid and propionic acid or mixtures thereof.

29. An inhalable solution or suspension according to claim 25, which contains at least one co-solvent or excipient.

30. An inhalable solution or suspension according to claim 29, containing a co-solvent selected from co-solvents which contain hydroxyl groups or other polar groups.

31. An inhalable solution or suspension according to claim 29, containing a co-solvent selected from isopropyl alcohol, propyleneglycol, polyethyleneglycol, polypropyleneglycol, glycolether, glycerol, polyoxyethylene alcohols and polyoxyethylene fatty acid esters.

32. An inhalable solution or suspension according to claim 29, containing an excipient selected from surfactants, stabilisers, complexing agents, antioxidants and/or preservatives, flavorings, pharmacologically acceptable salts and/or vitamins.

33. An inhalable solution or suspension according to claim 32, containing a complexing agent selected from editic acid or a salt of editic acid.

34. An inhalable solution or suspension according to claim 33 containing sodium edetate.

35. An inhalable solution or suspension according to claim 32, containing an antioxidant selected from ascorbic acid, vitamin A, vitamin E and tocopherols.

36. An inhalable solution or suspension according to claim 32, containing a preservative selected from cetyl pyridinium chloride, benzalkonium chloride, benzoic acid and benzoates.

37. An inhalable solution or suspension according to claim 29, containing, in addition to the substances **1** and (**2**) and the solvent, only benzalkonium chloride and sodium edetate.

38. An inhalable solution or suspension according to claim 29, containing, in addition to the substances **1** and (**2**) and the solvent, only benzalkonium chloride.

43. A method of treating an inflammatory or obstructive disease of the respiratory tract comprising administering to a patient in need of such treatment a therapeutically effective amount of a pharmaceutical composition according to claim 1.

44. A composition according to claim 1, further comprising a pharmaceutically acceptable organic or inorganic acid.

EVIDENCE APPENDIX

[none]

RELATED PROCEEDINGS APPENDIX

(None)